A CRITICAL REVIEW OF FRAILTY AND ACUTE CARE: RECOMMENDATIONS FOR FURTHER RESEARCH

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ABSTRACT

There is general agreement that frailty is a state of heightened vulnerability to stressors arising from impairments in multiple systems leading to declines in homeostatic reserve and resiliency. Yet unresolved questions persist about its detection and relationship with aging, disability and multimorbidity. This is particularly so in relation to our understanding of frailty among older patients presenting to acute care settings and the complex bidirectional relationship between frailty and hospitalization.

Building on the deliberations of a recent Canadian expert consultation meeting and a scoping review of the relevant literature between 2000 and 2015, this discussion paper presents a comprehensive review of the current state of knowledge on the detection of frailty in the acute care setting and its interrelationship with hospitalization. It concludes with a series of consensus recommendations regarding future research priorities in this important area.

INTRODUCTION

There is general agreement that frailty is a state of increased vulnerability to stressors arising from impairments in multiple body systems leading to declines in homeostatic reserve and resiliency (1). However, unresolved questions persist about its detection, pathophysiology, and relationship with aging, disability, and multimorbidity.

An area of uncertainty is the complex bidirectional relationship between frailty and acute care admissions. While frailty increases the risk of hospitalization, admission to acute care in turn is associated with the development of new or worsening frailty. The latter might be at least partially mediated by the changes in body composition and strength that can occur rapidly during hospital stays (2). Hospitalizations are a major contributor to the health care costs associated with frailty (3) and represent a dangerous period for this vulnerable patient population. Frail older patients are particularly susceptible to the adverse consequences of an acute care stay. Compared to more resilient patients they might benefit from a different approach to their care both during their hospital stay and after discharge (4) that could decrease the personal and societal burden of this health state. The detection of frailty might provide opportunities to refine or target intensive forms of therapy such as admission to an intensive care unit (ICU), surgery, chemotherapy, and invasive cardiac procedures (5-8) to patients most likely to benefit from them.

This discussion paper presents a comprehensive review of the current state of knowledge on the interrelationship of frailty and acute care, and offers consensus recommendations regarding future research priorities in this important area.

METHODS

This discussion paper evolved from a book chapter on the topic (9), the deliberations of a Canadian Institutes of Health Research (CIHR) funded invitational expert consultation meeting on *Frailty in Acute Care* held May 2-3, 2014 in Banff, Alberta (see **Appendix A** for attendees), and a scoping review (10) of key publications on frailty and acute care. To identify relevant studies, a series of PubMED searches were conducted by D.B.H. and C.J.M. prior to the consultation meeting. The searches were limited to English language articles published between January 2000 and April 2014. Subsequent to the consultation meeting these searches were updated every three months to identify potentially relevant studies published between May 2014 and November 2015. Papers dealing with frailty and the hospitalization of middle-aged and older persons (ages 50+ years) were selected for full review with results summarized. Their reference lists were also searched for relevant publications.

Findings based on the work done up to the end of April 2014 were presented at the expert consultation meeting. Participants were clinical, health services and epidemiological researchers with well-established track records and networks with the necessary expertise to advance the scope and quality of frailty research and knowledge dissemination (11). Three trainees under the supervision of an attendee also took part in the meeting. Participants were asked to share their work on this topic and present their perspective on the identification of frailty and the relationship(s) between frailty (however operationalized), hospitalization, and the ability of an older person to tolerate interventions.

This discussion paper is organized to reflect the key themes that emerged from the meeting and accompanying reviews. The first three sections cover approaches to the detection of frailty (in general and within acute care), frailty as a risk factor for hospitalization, and frailty as a prognostic factor for outcomes during and shortly after hospitalization. In the fourth section a number of special topic areas are addressed to highlight important gaps in knowledge and emerging research. Section five summarizes the implications of our review for both clinical care and research. We conclude with a number of consensus recommendations regarding research priorities for frailty and acute care.

1. DETECTION OF FRAILTY

A number of approaches to detection have been proposed with no consensus on which one to use (12). This may reflect the multifaceted nature of frailty in later life as well as the unique perspective taken by individual researchers - as Heisenberg noted, "what we observe is not nature in itself, but nature exposed to our method of questioning" (13) Two systematic reviews on the detection of frailty examined 22 and 27 measures respectively (14,15) with none identified as the preferred one.

Tables 1 and **2** provide a summary of commonly used approaches to detect vulnerable older adults in acute care settings. They (and others not noted) vary markedly. The most appropriate approach for detection is dependent on the specific purpose(s) of the investigator, the population being studied, the clinical or research setting, the timing of the evaluation, the available data, and the experience and training of the assessor.

The first category includes judgment-based measures. They include "eyeball" or "end-of-the-bed" assessments (16) where clinicians express an opinion on whether the patient is

frail. The validity of this approach is upheld by the belief that clinicians can recognize frailty when they see it (even if they can't fully explain how) (17). The reliability of these determinations when no pre-specified criteria are used is questionable. There are concerns about the influence of personal biases such as equating frailty with obvious physical features (e.g., how old the person looks, female sex, slight build), which could downplay if not entirely omit consideration of important dimensions such as cognition and psychosocial attributes. Inter-rater reliability of judgment-based assessments are good when they are performed by practitioners experienced in the care of older patients but less so when the determination is done by less experienced clinicians without specific training (18). Some judgment-based determinations (e.g., the *Canadian Study of Health and Aging [CSHA] Clinical Frailty Scale* [see **Table 1**]) provide clinicians with descriptions or images that aid in placing patients on a fitness-to-frailty ordinal scale (19).

The second category includes physical performance measures such as gait speed, grip strength, or chair stands within a defined period of time (20). Among these, gait speed (e.g. measured at a comfortable pace over 4-5 m from a standing start) has been proposed as a practical, objective, and easy to interpret measure that accurately predicts important health outcomes (21). Among community-dwelling seniors, velocities less than 0.8 m/sec are associated with higher risks of poor health and death (22,23). Aside from self-selected pace, other gait parameters (e.g., variability, cadence, step width and length, time in double support, dual-task speed) might be used to detect and grade frailty (24). A limitation to performance-based measures is the relatively high proportion of older adults, particularly those with significant cognitive and functional limitations (who many would argue are

frail), unable to complete these measures (25,26). As well their limited specificity detracts from their accuracy as a stand-alone test for frailty (27).

The third category includes multi-dimensional measures of physical frailty. The most commonly used example of this approach is the *Cardiovascular Health Study (CHS) frailty criteria* (15,28). Here frailty is deemed present if the person has three or more of the following five factors: weak grip strength, slow walking speed, low level of physical activity, complaints of fatigue/ exhaustion, and unintentional weight loss. These criteria have been criticized as solely measuring physical frailty with important domains such as cognition and mood not assessed (1,26). Other composite physical frailty measures include:

1. *Study of Osteoporotic Fractures* (*SOF*) frailty index (i.e., 2 or more of: weight loss of > 5% in the past year, inability to rise from a chair 5 consecutive times without using arms, and a reduced sense of energy) (29)
2. *Short Physical Performance Battery* (i.e., comprised of 3 tests of lower body function [timed 8-foot walk, 5 timed chair stands, hierarchical test of standing balance] each scored 0-4) (30)
3. *SHARE-FI* (i.e., based on grip strength, presence of fatigue, loss of appetite and/or eating less than usual, difficulties climbing stairs and/or walking 100 m, and a low level of physical activity) (31).

The fourth category comprises multi-dimensional instruments that incorporate domains in addition to physical performance. Their use is supported by a general agreement among experts that frailty is multidimensional and may involve cognitive, emotional, social, and/or spiritual aspects as well as physical components (32). An example is the *Edmonton*

Frail Scale (EFS), which includes cognition, instrumental activities of daily living (IADL), burden of illness, self-rated health, mood, nutrition, medication issues, incontinence, social support, and mobility (33). Other multi-dimensional instruments include:

1. *FRAIL* (3 or more of fatigue, walking up stairs, walking a block, presence of more than 5 illnesses, and weight loss) (34)
2. *Frailty Trait Score* (frailty determination based on an assessment of energy balance and nutrition, activity, nervous system, vascular system, weakness, endurance, and slowness) (35)
3. *FI-CGA* (where a comprehensive geriatric assessment or CGA [a multidimensional, interdisciplinary diagnostic process to determine the medical, psychosocial, and functional capabilities of the patients in order to develop a coordinated and integrated care plan] incorporating 10 scored (0 to 3) and totaled domains [cognition, mood and motivation, communication, mobility, balance, bowel function, bladder function, IADLs and ADLs, nutrition, and social resources] is used) (36)
4. *Groningen Frailty Indicator* (consists of 9 physical, one cognitive, 3 social, and 2 psychological factors) (37)
5. *Tilburg Frailty Indicator* (with 8 physical, 4 psychological, and 3 social components) (38).

The latter was derived from the work of the Canadian Initiative on Frailty and Aging (39). One of the challenges with these instruments is that they differ in the type and number of domains included, how they are assessed, and the weighting of factors within and across domains. This leads to identifying overlapping, but distinct, sub-groups of patients.

The last category, and second most commonly used approach in the research literature, involves the derivation of a measure termed a *frailty index* [*FI*] (15,40). Here 30 or more health "deficits" (i.e., symptoms, signs, diseases, disabilities, and/or laboratory abnormalities) are identified and summarized as a single score. The items selected should be associated with health status, cover a range of systems, and generally increase with age but not saturate (have a very high prevalence) at older ages. The *FI* of a person is the ratio of deficits present to the total number considered. For example, if 10 of 40 possible deficits were found in a given person, their *FI* would be 10/40 or 0.25. Rather than taking a dichotomized approach (i.e., frailty is present or not), a *FI* is often treated as a continuous variable allowing one to consider grades of severity. This approach is based on the premise that the more things wrong, the more likely a person is frail. However, it has been criticized for the large number of factors requiring consideration and its mathematical nature (26). Along with other frailty measures, the *FI* does not explain how frailty develops or fully inform approaches to its prevention or management (41).

With regard to the approaches summarized above, a few additional issues warrant further consideration. The distinction between a *FI*, a multidimensional instrument and a judgment-based approach is not always clear. All of these can be based on the same data such as the findings from a CGA (19,36,42,43). Another issue is the distinction between frailty and disability. The *CSHA Clinical Frailty Scale*, a number of the multi-dimensional instruments, and many of the derived *FI* measures include measures of disability in their scoring. Including disability measures in the identification of frailty goes against the belief of many that the two are distinct though overlapping concepts (44). Looking for those requiring help in activities of daily living has been recommended as the most practical way

of identifying frail patients in hospital (45). This raises several questions, specifically, why call it frailty when what you are detecting is disability and what is driving any risk discovered with the state – disability or frailty?

Detection of Frailty in Acute Care

Frailty affects 20-50% of older patients in hospital with the exact figure influenced by the approach taken for identification (46). For example, in five studies reporting on the prevalence of frailty among older patients hospitalized with cardiac problems, prevalence ranged from 4 to 63% (47-51). Though there were other sources of variability (including significant differences in the age of participants and underlying cardiac conditions), these studies used different methods for the detection of frailty.

Rarely are patients admitted to hospital with a diagnosis of frailty. An exception might be for elective surgery as the pre-operative assessment could include a search for frailty. Gait speed determined before surgery has been used as a measure of frailty in older patients undergoing cardiac surgery (47). It was found that slower walkers (speed < 0.83 m/sec) were more likely to encounter adverse outcomes. Similar findings were seen in a study of patients with coronary artery disease undergoing cardiac catheterization where slower gait speed (< 0.65 m/sec) was a strong predictor of 6-month mortality (49).

Detection after admission should be based on criteria validated in this setting. Some of the methods developed for identifying frailty in community-dwelling individuals such as the *CSHA Clinical Frailty Scale* and the *CHS frailty criteria* have been successfully used in acute care. A reported version of the *EFS* was developed for use by non-geriatricians (52). Results correlated moderately well with frailty determinations made by geriatricians and

could be reliably administered. Higher reported *EFS* scores among older general medical patients were associated with longer lengths of stay and discharge destination (53). A brief frailty battery (i.e., balance measure, Body Mass Index, Trail-Making Test Part B, a depression questionnaire, determination of whether the person lives alone) specifically developed for older patients undergoing cardiac catheterization was found to be both feasible and predictive of subsequent increases in disability and declines of health-related quality of life (51). Gait speed did not perform as well as balance in this study, partly due to the difficulties in measuring it in patients with intravenous catheters. Balance measures like one-leg standing have been suggested as potential frailty markers (54). Alternative approaches would include questionnaires (e.g., *FRAIL*) and using existing health record data to derive a *FI* such as was done with the interRAI assessment system for acute care (55).

Frailty is a dynamic state with transitions between non-frail, pre-frail, and frail categories over time (56-58). While transitions as people age are generally towards higher degrees of frailty severity, improvement can also occur. Gill et al reported that the chances of moving from a greater to a lesser degree of frailty were reduced by approximately 50% with each hospitalization (4). Less striking effects for hospitalization were seen with the development of more severe degrees of frailty, but it was uncommon to move from the non-frail to a frail state without at least one intervening hospital admission. Investigations reporting on frailty trajectories during care transitions are currently scarce as are estimates of the sensitivity of frailty measures to change. While transitions across frailty states may be attributable to the health conditions leading to admission, there are intrinsic hazards with hospitalization for older persons (59). There has been recent interest in what has been

termed the *post-hospital syndrome*. This is an acquired condition of transient heightened vulnerability after hospitalization (60-62) that is felt to arise from the synergistic effects of the presenting problem, comorbidities, and the toxicities of the hospital environment (e.g., immobility, sleep deprivation, polypharmacy, poor nutrition, uncontrolled pain, secondary illnesses, iatrogenic events). Whether frail individuals are more susceptible to the *post-hospital syndrome* is suspected but not known.

Irrespective of the approach used, screening for frailty in acute care should satisfy Wilson and Jungner criteria before wide adoption (63). Key questions that need to be addressed regarding the utility and feasibility of doing this are listed in **Table 3**.

2. FRAILTY AS A RISK FACTOR FOR HOSPITALIZATION

As a state of heightened vulnerability, frailty could be predicted to increase the risk of hospitalization; however it has attracted less interest than other outcomes (14). Notably, the expected association between frailty and hospitalization might be modified by other factors, such as competing risk of death, substitution effects, and advance care planning. In one study the proportion of frail older men residing in assisted living settings who were hospitalized did not differ significantly from non-frail residents (64). This was potentially due to their high mortality, which led to their removal from the "at-risk" pool. Long-term care placement, a relatively common outcome for frail older adults, can lead to a substitution or replacement effect for acute care due to factors such as the availability of nursing care (65). In a study of end of life health care costs, older adults dying with a frailty trajectory (i.e., slow steady decline during the period before death) had lower hospital but greater long-term care expenditures compared to those where death arose from organ

failure or a terminal illness (66). In acutely ill older adults with more severe frailty, a decision may be made to provide care focusing on the relief of symptoms and avoiding hospitalization (67). Creating alternatives to hospital-based care for the management of acute illnesses is an active area of development (68).

Most but not all studies indicate that frailty, however defined, increases the risk of hospitalization. The paper initially describing the *CHS frailty criteria* reported that over three years, 33% of non-frail study participants were admitted to hospital compared to 43% of pre-frail and 59% of frail subjects ($p < 0.0001$) (28). While the Women's Health and Aging Study using modified *CHS frailty criteria* did not find this association (69), heightened risk was evident in the National Health and Aging Trends Study where overnight hospitalization over the previous 12 months occurred in 11.1% of non-frail, 22.1% of pre-frail, and 42.4% of frail subjects ($p < 0.001$) (70). The presence of *SOF* defined frailty increased the odds for hospitalization over the next year approximately two-fold (2.08, 95% CI 1.02-4.24, $p=0.045$) (71). A higher risk of 1-year hospitalization was found for older community-dwelling individuals with slow gait speed (41% of those with a gait speed of < 0.6 m/sec were hospitalized at least once compared to 26% for those with a gait speed of 0.6 to 1.0 m/sec and 11% if > 1.0 m/sec, $p < 0.0001$) (72). A higher value on a 30-item *FI* based on data from the Canadian Community Health Survey was associated with a significantly increased risk of hospitalization, multiple hospitalizations, and an emergency hospitalization over the subsequent 18 months (73). Frailty has also been linked to a higher likelihood of being hospitalized with specific conditions like heart failure (74) and end-stage renal disease (75).

Possibly due to the factors previously noted, the positive association between frailty and subsequent hospitalization tends to be weaker than that seen with mortality (76,77). Frailty has been shown to add relatively little to predictive models that include age, sex, and multimorbidity (76). A similar muted contribution of frailty to predictive models for disability is seen (78).

Few studies have directly compared frailty measures in their ability to predict hospitalization. The *SOF* and *CHS criteria* had similar abilities in one study (79), while a multi-dimensional scale (*Conselice Study of Brain Aging Index*) performed better than the *SOF* in another (80). No significant differences were seen between *CHS criteria* and two *FI*s in their ability to predict hospitalization among assisted living residents (76). In light of the paucity of data, it remains unknown whether a particular approach performs significantly better in this respect.

3. FRAILTY AS A PROGNOSTIC FACTOR FOR OUTCOMES DURING AND POST-HOSPITALIZATION

Frail patients generally take longer to recover from an acute illness, have longer lengths of hospital stays, are more likely to be discharged to a higher level of care, and are at increased risk of complications and readmission. Older hospitalized patients with a myocardial infarction and frailty assessed using the *CSHA Clinical Frailty Scale* had a significantly longer average length of stay with higher risks for in-hospital and one-month mortality and a composite outcome consisting of death, re-infarction, revascularization procedure, re-hospitalization, major bleeding, cerebrovascular disease, and/or need for dialysis (81). Another study that looked at outcomes after cardiac surgery found that slow

gait speed was associated with an increased risk of a prolonged postoperative stay and a higher likelihood of mortality, major morbidity, and/or discharge to a health care facility (47). Patients with frailty as assessed with modified *CHS criteria* had longer lengths of stay after both minor and major surgical procedures, experienced higher rates of post-operative complications and were more likely to be discharged to an assisted living facility (48). Increasing levels of frailty identified with the *EFS* in older surgical patients were associated with longer lengths of stay, more post-operative complications, and a lower likelihood of being discharged home (82). A multi-dimensional frailty instrument based on data collected during a pre-operative assessment was associated with a higher likelihood of death and institutional discharge as well as greater health care costs (83-85). In an Australian study of older people hospitalized with an acute illness, the *CSHA Clinical Frailty Scale* predicted in-hospital mortality, new nursing home placement, and a longer hospital stay (86). A large UK study found that a modified *CSHA Clinical Frailty Scale* (i.e., 9-point version) in adjusted analyses was an independent predictor of in-patient mortality, transfer to the geriatric service, and a length of stay of 10 or more days (87). Another study using the 9-point version of the scale reported that moderate to severe frailty was an independent predictor of readmission to hospital or death within 30 days of discharge (adjusted OR 2.19, 95% CI 1.12-4.24) (88).

Delirium is a common and serious complication for hospitalized older patients (89). Most but not all studies indicate that frail older hospitalized patients are more likely to develop delirium. Two studies reported an increased risk of developing postoperative delirium (90,91). A third one that dealt with patients seen by a geriatric medicine service suggested frailty increased the likelihood of not fully recovering from a delirium (92). While a recent

paper found that physical frailty was not a risk factor for delirium in older patients admitted to an acute geriatric ward (93), a prospective observational study of elective cardiac surgery patients reported that frailty (whether identified by a physical performance measure, modified *CHS criteria*, or a *FI*) was associated with a 3- to 8-fold increase in the risk of post-operative delirium (94). It has been speculated that there is a mutually reinforcing relationship between the two with frailty predisposing to delirium and delirium decreasing the likelihood of recovering from hospitalization (95).

In older persons, hospitalization increases the likelihood of developing new or worsening disability (96). It was initially unclear whether frail patients showed greater functional decline than non-frail ones (97). Boyd et al reported that the development of increasing dependency in ADL after hospitalization was more likely among those with pre-existing frailty based on *CHS criteria* (98). Gill and colleagues found that the likelihood of "transitioning" from none to mild disability within a month of hospitalization was 34.9% (95% CI, 34.5%-35.3%) for physically frail individuals compared to 4.9% (95% CI, 4.7%-5.1%) among non-frail ones (56). Functional decline from pre-admission status at the time of hospital discharge has also been used to retrospectively diagnose frailty in older patients (99,100). A study that tracked mobility in older patients during their hospital stays found that those with higher scores on a *FI* had slower rates of recovery and lower levels of performance both on admission and after 2 weeks in hospital (101).

Attempts have been made to use claims data for the detection of frailty. As examples, its presence has been determined in several studies by evidence of a nursing home stay and/or a physician claim for a diagnosis that is felt to be associated with frailty (102-104).

While further research is needed on the validity of the measure, older adults admitted to an ICU categorized as frail by claims data had higher hospital and 3-year mortality than non-frail individuals (104). Another study reported a significantly higher 1-year postoperative mortality among individuals categorized as frail using diagnoses recorded in health administrative data (105).

4. SPECIAL TOPICS

Our literature review and deliberations identified a number of emerging research areas relevant to an exploration of the relationship between frailty and acute care. They are briefly examined in the following sections.

I. Geriatric Trauma: Frailty is a way to appreciate the heterogeneity of older patients who experience significant trauma (106). A *FI* independently predicted in-hospital complications (odds ratio [OR] 2.5, 95% CI 1.5-6.0, p = 0.001), discharge to a skilled nursing facility or death in hospital (for the latter two outcomes combined the OR was 1.6, 95% CI 1.1-2.4, p = 0.001) among older trauma patients (107,108). The same investigators reported that a 15-item frailty scale was an independent predictor in adjusted analysis of discharge to a skilled nursing facility or death (109). Among older patients admitted after ground-level falls, frailty (identified by a *FI* of 0.25 or greater) in multivariate analyses identified patients more likely to have fractures (OR 1.8, 95% CI 1.2-2.3) and be discharged to a facility (OR 1.42, 95% CI 1.08-3.09) (110). It has been proposed that frailty assessments might have a role in anticipating the discharge needs of these patients.

II. Intensive Care Units: Utilization of intensive care units (ICUs) by very old (aged 80+ years) patients is rising (111). Their probability of surviving and returning to baseline

levels of functioning at 1 year after ICU admission is approximately 26% (112). Pre-ICU frailty assessments have attracted interest as a potential prognostic factor (113). Bagshaw et al reported a 32.8% prevalence of frailty based on the *CSHA Clinical Frailty Scale* in critically ill patients (aged 50+ years) admitted to participating ICUs across the province of Alberta, Canada (114). In adjusted analyses, both in-hospital and 1-year mortality were higher among frail patients. They were also more likely to suffer major adverse consequences, become functionally dependent, report a lower quality of life and be readmitted to hospital in the 12 months following presentation. In another multicenter study of older ICU patients, a frailty prevalence of 23-41% based on different approaches was reported (115). In this study the *CSHA Clinical Frailty Scale* outperformed modified *CHS criteria* in predicting hospital and 6-month mortality. Judgment-based determinations of pre-morbid status like the *CSHA Clinical Frailty Scale* are appealing due to the inability of many ICU patients to perform physical tests at the time of their admission (5). It may also be feasible to derive a *FI* utilizing previously collected data on these patients. In a specialized geriatric ICU a *FI* constructed from variables drawn from the ICU admission records was strongly associated with likelihood of survival (116). While frailty assessments can be used to frame and manage the expectations of both patients and their families, it seems premature to advocate their use in decision-making about the withdrawal of treatment (115,117). Frailty determinations may eventually guide multi-factorial interventions targeting the underlying biological basis for a given individual.

III. Surgery: Frailty has attracted increasing interest as a predictor of surgical outcomes (6,118). As examples, a frailty scale based on a CGA performed before surgery predicted postoperative 1-year all-cause mortality and discharge to a nursing facility in adjusted

analyses (119), and a 5-point frailty risk score consisting of two components of *CHS criteria* (weight loss, grip strength), American Society of Anesthesiologists (ASA) scale score, and hemoglobin predicted 30-day postoperative complications (120). In the future, frailty assessments might be used to tailor the anesthetic and surgical (including deciding whether to operate) approach, counsel patients about likely outcomes, and trigger the implementation of select preoperative (e.g. physical therapy, nutritional supplements) and perioperative (e.g., team-based pathways, delirium prevention) strategies (118).

IV. Oncology: Within this decade persons 65 years of age and older are projected to account for 70% of all cancer diagnoses (121). Older persons with a non-skin cancer appear to have a higher prevalence of frailty compared to those without such a history (122). The mechanisms underlying this relationship are unclear. Both cancer and frailty have common manifestations. Symptoms such as weight loss and fatigue, which are felt to be clinical markers of frailty, become common during the later stages of cancer. Cachexia associated with cancer and other chronic diseases and age-related sarcopenia represent two distinct muscle wasting conditions that lead to declines in muscle mass, strength, and function (123,124). Additional research is needed to better understand these two processes, how they overlap and interact, and what can be done to counteract them. It is also possible that cancer and its treatment could lead to frailty. Childhood cancer survivors might be predisposed to frailty from the toxic effects on normal tissue of the multimodal therapy used to treat their malignancy. The prevalence of frailty based on modified *CHS criteria* among these survivors in a study was equivalent to cohorts about 30 years older and associated with an increased risk of death (125). A research priority in geriatric oncology is the identification of vulnerable patients who superficially appear healthy

enough for aggressive forms of therapy yet are at high risk of decompensation (7). Better delineation of this group could inform the choice of treatment options though additional work on this is clearly needed. In a pilot study of patients newly diagnosed with cancer, frailty markers were commonly found but did not predict subsequent health care utilization (126), although weak grip strength was associated with developing severe treatment toxicity (127).

V. Cardiovascular Disease: The relationship between frailty and cardiovascular disease might be due to common causal pathways such as chronic low-grade inflammation and insulin resistance (8). In addition to the methods previously described, other approaches for identifying frailty in this patient population have been utilized such as the *Comprehensive Assessment of Frailty* test (128), an abridged version called *Frailty predicts death One yeaR after Elective Cardiac Surgery Test* (*FORECAST)* that consists of timed chair stands, self-reported weakness and ability to climb stairs, the *CSHA Clinical Frailty Scale*, and serum creatinine (129), and a *FI* measure (130). Preoperative gait speed and the *CSHA Clinical Frailty Scale*, though, have attracted the greatest interest as a way to screen for frailty in patients with cardiovascular disease. Information of frailty status could be used to both predict risk and possibly direct therapy (8,131,132). The benefit of tailoring therapy based on a frailty determination awaits verification, but it holds great promise as a means of improving the care provided to vulnerable patients (133).

VI. Chronic Kidney Disease: The prevalence of frailty in patients with chronic kidney disease (CKD) not currently on dialysis therapy has been studied using modified *CHS criteria*. Patients, even at an early stage of renal dysfunction (i.e., CKD stage 1 or 2), have an

approximately 2-fold higher risk of frailty with the likelihood of frailty rising with increasing degrees of renal dysfunction (134). Frailty is associated with worse outcomes in patients with CKD. There is an approximately 2-fold increased risk of mortality or dialysis in older patients with renal impairment after adjusting for potential confounders (134). Frailty based on modified *CHS criteria* affects about three-quarters of patients starting dialysis (135) and is associated with higher estimated glomerular filtration rate (eGFR) at initiation (possibly because frailty symptoms are judged as those of uremia, eGFR in the setting of low muscle mass overestimates true GFR [meaning initiation at a higher eGFR is appropriate], and/or greater willingness of frail patients to start dialysis). After initiation of dialysis, frail patients have a greater likelihood of dying and a higher risk of hospitalization compared with non-frail patients. Frailty might be a factor for consideration when deciding on a non-dialytic or conservative approach in patients with advanced CKD (136), though research suggests that frailty might be at least partially reversible in this patient population. Among recipients of a kidney transplant who met *CHS criteria* for frailty, nearly three-quarters were non- or intermediately frail 3 months post-procedure (137).

VII. Medications: The use of multiple medications concurrently (i.e., polypharmacy) is common among frail persons (138-141), as is the use of sedating or anticholinergic drugs (142-144). Observational studies show an association between polypharmacy and both these drug classes with the subsequent development of frailty (140,142,145). There are potential changes in the distribution, binding, metabolism, transport, and/or elimination of pharmaceuticals associated with frailty (146-151). This is not to say that frail individuals cannot benefit from pharmacotherapy. Secondary analysis of HYpertension in the Very Elderly Trial (HYVET) data found no evidence of an interaction between treatment effect

and a *FI* (152). The complicated benefit/risk analyses required with the pharmacotherapy of frail patients were shown by a study on antithrombotic therapy in older hospitalized patients with atrial fibrillation (153). Compared to non-frail patients those with frailty were significantly less likely to be discharged on warfarin ($p < 0.0001$), more likely to have a cardio-embolic stroke within six months (12.3% versus 3.9%, $p < 0.05$), and showed a non-significant trend for more major or severe hemorrhages (23.0% versus 16.9%, $p = 0.29$). While oral anticoagulants may offer the best hope of stroke prevention, this has to be tempered by a possible increase in bleeding risk and a narrowing of the therapeutic window (154). Although not well investigated, medications (e.g., angiotensin converting enzyme inhibitors, vitamin D, anabolic hormones, ghrelin) have also been considered as potential therapy for frailty (155,156).

5. IMPLICATIONS FOR CLINICAL CARE AND RESEARCH

Multiple studies across a range of settings have shown that frailty (variously defined) is associated with adverse outcomes. Additional studies solely demonstrating this would be redundant unless they compare alternative ways of identifying frailty or contrast frailty with non-frailty measures in predicting outcomes. There are more pressing research needs in confirming the clinical utility of frailty in counseling patients about their care and developing (and evaluating) interventions to prevent or slow further declines.

Patents with frailty, especially at a later or more severe stage (i.e., presence of disability and/or life-threatening illness), are less likely to benefit from more intrusive forms of therapy and can be reasonably advised to consider a less aggressive course of action (157). While the detection of frailty should trigger these person-centered discussions (158),

caution should be exercised in using frailty as the reason to withhold potentially beneficial forms of therapy (159). While it has been suggested that "frailty" is a euphemism for patients who are terminally ill (160), in individual patients it may be partially reversible (137,158). Advice given to patients and their families should be based on a comprehensive individualized review that considers the possibility of modifiable contributors. Accurate information on the relative benefits and risks (including burden) of available therapies is needed for informed decision-making (158,161). Even if associated with a higher mortality, a particular intervention might still be preferred by a patient if it offered the best hope for "success" as viewed by the patient. In this context, outcomes such as symptom control, independence, and quality of life may be judged of greater relevance than mortality.

Adding frailty to characteristics like age, sex, multimorbidity, Probability of Repeated Admission (Pra) questionnaire (162), and/or the American Society of Anesthesiologists (ASA) score (163) increases the areas under receiver operating characteristic (ROC) curves for predicting patient outcomes, but the gains are relatively modest (0.012 to 0.073) (48,64,72). There is still debate about the clinical utility of frailty assessments (77,164,165) and uncertainty as to whether frailty adds to the prognostic abilities of multimorbidity and/or disability measures. For example, Aarts et al in a population-based cohort found that while *CHS criteria* defined frailty was associated with an increased risk of both death and institutionalization this risk was limited to those who also had multimorbidity and/or disability (166). In a second study Ferrante and colleagues assessed the "functional trajectories" (based on a count of basic, instrumental, and mobility disabilities) of older patients who had at least one ICU admission. Compared to those with minimal pre-ICU disability, patients with mild-to-moderate and severe pre-existing disability had more than

double and triple the risk respectively of dying within a year. Physical frailty based on gait speed was not a significant contributor to mortality risk in adjusted analyses (167).

Recommendations for the management of frail older patients in hospital (168,169) include CGA (referred to as the "gold standard for the management of frailty in older people") (158), tailored interventions provided in a defined physical environment (e.g., Acute Care for Elders [ACE] units), universal processes to enhance recovery (e.g., early mobilization), screening for common problems (e.g., delirium), minimizing challenges to older patients that might precipitate problems or impede recovery (e.g., Hospital Elder Life Program), and/or pro-active discharge planning. While the utility of CGA is supported by the literature (170), its effects (and those of other in-hospital interventions on patient outcomes) have been modest (171). No relationship was found between a measure of higher quality of care while in hospital and the likelihood of functional decline after discharge (172). To have a significant impact, a fundamental change in the structure and processes of the care provided in hospital is likely needed (173). At this time few randomized controlled trials (RCTs) of interventions for frailty have been done or are ongoing (174,175).

Avoiding admissions or decreasing exposure to the hazards of hospitalization by earlier discharges would complement in-hospital approaches (176-179). Improved coordination of services and shifting resources to the community could lead to more efficient use of acute care services (3). An intriguing finding in the controlled trials of hospital-at-home programs has been a lower incidence of delirium among home-treated patients (180-183). Delirium might function as a marker of the stresses placed on vulnerable older patients.

Attempts to "reactivate" frail patients after hospitalization is potentially promising (184), but a RCT of year-long home exercises in a relatively fit group of older women who suffered a hip fracture failed to show functional gains with the intervention (185). Whether a frail group might have benefitted is an unanswered question.

Table 4 summarizes our consensus recommendations for research on frailty and acute care. This work is required before we can achieve a fuller understanding of how the recognition and management of frailty could improve both the utilization of hospital care by vulnerable populations and, most importantly, their outcomes.

DECLARATIONS

List of abbreviations

CGA Comprehensive Geriatric Assessment
CHS Cardiovascular Health Study
CI Confidence Interval
CIHR Canadian Institutes of Health Research
CKD Chronic Kidney Disease
CSHA Canadian Study of Health and Aging
EFS Edmonton Frail Scale
FI Frailty Index
IADL Instrumental Activities of Daily Living
SHARE Survey of Health, Ageing and Retirement in Europe
SOF Study of Osteoporotic Fractures

Ethics approval and consent to participate

Not applicable.

Competing interests

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Authors' contributions

DBH, CJM, SB, SEB and BH made substantial contributions to the conception and design of the work and acquisition of funding. DBH and CJM drafted the initial versions of the manuscript and were involved in revising it critically for important intellectual content. JA, RCA, SB, JB, HB, SEB, ED, BH, KM, AM, DR, TS, HTT and HW made substantial contributions to conception and design of the manuscript and revised it critically for important intellectual content. All authors approved of the final version submitted for review and agreed to be accountable for the content presented.

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Table 1: CSHA Clinical Frailty Scale (19)

1. **Very fit** – robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the fit group for their age.
2. **Well** – without active disease, but less fit than people in category 1.
3. **Well with treated co-morbid disease** – disease symptoms are well controlled compared to those in category 4.
4. **Apparently vulnerable** – although not frankly dependent, these people commonly complain of being "slowed up" or having disease symptoms.
5. **Mildly frail** – with limited dependence on others for instrumental activities of daily living.
6. **Moderately frail** – help is needed with both instrumental and non-instrumental activities of daily living.
7. **Severely frail** – completely dependent on others for activities of daily living or terminally ill.

Table 2: Detection of Frailty in Acute Care Settings – A Summary of Frailty Measures

Characteristic	Judgment-based Measure	Physical Performance Measure	Physical Frailty	Multi-dimensional Frailty	Frailty Index
Description	Determination of frailty based on the judgment of a clinician	Use of a single physical performance measure to categorize patients	Based on a belief in a frailty phenotype; frailty defined as being present if a certain number of criteria are present (rules based)	Extension of physical frailty to include other dimensions (e.g., cognition, disability/ function, psychological state, morbidities, self-rated health, sensory deficits, social)	Assesses the accumulation of deficits predisposing to adverse outcomes; calculated as total number of items (deficits) present divided by maximum potential number
Number of Items	1	1	3-5	5-20	30+
Examples	"Eyeball" or "end-of-the-bed" subjective assessment (16,17); Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale (19); Subjective Frailty Score	Chair stands; gait speed; grip strength (20-24)	Cardiovascular Health Study (CHS) criteria (15,28); Study of Osteoporosis Fractures (SOF) scale (29); Survey of Health, Ageing and Retirement in Europe Frailty Index (SHARE-FI) (31)	Conselice Study of Brain Aging (CSBA) index; Edmonton Frail Scale (33); Fatigue, Resistance, Ambulation, and Loss (FRAIL) (34); derived from a standardized comprehensive geriatric assessment (FI-CGA) (36); Frailty Trait Scale (FTS) (35); Gérontopôle Frailty Screening Tool; Groningen Frailty Indicator (37); Tilburg Frailty Indicator (38)	Frailty Index [FI] (various iterations) (15,40)
Comments	Subjective assessments open to potential bias and concerns about reliability; can be based on multidimensional frailty assessment	Quick and easy to perform (though may require equipment); similar to physical frailty; doesn't capture complex nature of	Widely use; doesn't capture the notion of frailty as a continuum; criticized for excluding non-physical domains	Uncertainty of which dimensions to include, how to assess and then combine them; scales utilizing different domains identify	Criticized as containing too many items with issues of feasibility; unclear it has clinically significant advantages to

		frailty; impairments may be due to factors other than frailty; many older patients unable to complete testing		different sub-groups; with increasing item number becomes similar to frailty index	simpler approaches

Table 3: Key Questions about the Utility and Feasibility of Frailty Assessments in Acute Care Settings.

1. Does frailty replace or add significantly to "traditional" risk factors like age, sex, disability, disease severity, and multimorbidity or to the variety of standardized and validated risk tools developed for specific clinical populations in determining prognosis or facilitating care planning?
2. In what situations or settings does frailty provide actionable information (i.e. specific and credible data that can be used to make recommendations or decisions about interventions)?
3. Is the proposed frailty measure feasible, reliable and valid when administered to acutely ill patients in the fast-paced hospital setting (given most instruments and frailty indices were initially developed and validated in community samples)?
4. For acutely ill patients in the hospital, is it possible (or even desirable) to successfully disentangle frailty from the effects of their presenting illness and its treatment?

Table 4: Research Priorities for Frailty and Acute Care

1. *A systematic review should be undertaken to determine whether older hospitalized patients should be screened for frailty.* While frailty is associated with a higher risk of both admission to hospital and adverse consequences arising during the stay, there continues to be debate about the clinical utility of its detection. Such a review should consider both the positive and the negative aspects of detecting frailty.
2. *The choice of the frailty measure to be used in a research study should be primarily based on the aim or intention of the investigators, specifics of the population being studied, psychometric qualities of the instrument, and questions of feasibility and respondent burden (186).*
3. *The relationship between frailty and the post-hospital syndrome should be explored.*
4. *Studies of frailty trajectories and outcomes should consider the potential modifying effect of psychosocial factors (187).*
5. *There is an urgent need to develop and evaluate interventions that will allow frail older patients to safely avoid hospitalization and/or receive improved care once admitted that will minimize adverse consequences and promote recovery to the greatest extent possible both during and after hospitalization.* A wide range of approaches should be considered including exercise/ physical activity, nutritional supplements, pharmaceutical agents, multidimensional interventions, and health system innovations. This will require the investment of targeted research funds.

6. *Further work is needed on exploring interventions to prevent the development and/or progression of frailty.* This holds the greatest potential of benefit at a population level.
7. *An interdisciplinary, intersectoral (i.e., community, acute care, long-term care) research network that meaningfully involves patients and families should be created and supported.*

Appendix A:
Attendees of invitational expert consultation CIHR planning meeting on Frailty in Acute Care held May 2-3, 2014 in Banff, Alberta:

Dr. Jonathan Afilalo (McGill University)
Dr. Rakesh C. Arora (University of Manitoba)
Dr. Sean M. Bagshaw (University of Alberta)
Dr. Jenny Basran (University of Saskatchewan)
Dr. Howard Bergman (McGill University)
Dr. Susan Bronskill (Institute for Clinical Evaluative Sciences)
Ms. Sima Gandhi (Institute for Clinical Evaluative Sciences)
Dr. Brenda Hemmelgarn (University of Calgary)
Dr. David B. Hogan (University of Calgary)
Dr. Kenneth Madden (University of British Columbia)
Dr. Tina Mah (Grand River Hospital)
Dr. Colleen J. Maxwell (University of Waterloo)
Dr. Arnold Mitnitski (Dalhousie University)
Dr. Darryl Rolfson (University of Alberta)
Ms. Kathryn J. Stock (Graduate Student)
Ms. Helen Tam-Tham (Graduate Student)
Dr. Hannah Wunsch (University of Toronto)

Invited consultants not able to attend:
Dr. Elijah Dixon (University of Calgary)
Dr. H. Tom Stelfox (University of Calgary)